Computational Toxicology 6 (2018) 1–8

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

A data-fitted mathematical sequence to calculate depuration rates for pesticide residues in milk from dairy cow feeding studies

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ARTICLE INFO

Keywords:
Livestock feeding
Pesticide residues
Milk
Mathematical sequence
Depuration

ABSTRACT

A mathematical sequence is introduced to extract information on the rate of pesticide residue level increase and decline in milk from dairy cows dosed, for a number of days, with pesticide in a livestock feeding study. The sequence is governed by two parameters: 1) the added increment of residue concentration attributed to the daily dose and, 2) the constant proportion of residue dissipated in a day. Values for the parameters are obtained by finding the best fit of the sequence to the measured residues in the milk. Behaviour of the residue in the depuration phase (after dosing has ceased) is well predicted by the parameters obtained from the dosing phase. Not all dairy cow feeding studies have included a depuration phase, so the data-fitted mathematical sequence supplies the previously lacking information.

Introduction

Livestock feeding studies provide the link between pesticide residue levels in the animals' diet and the resulting residue concentrations in meat, milk (dairy cow) and eggs (poultry). Such residue concentrations are needed for estimating maximum residue levels in food and for calculating possible human dietary exposure.

The requirements for livestock feeding studies and the necessary data to be obtained are described in the FAO Manual [1]. The OECD also provides guidance on the conduct of livestock feeding studies and pesticide residues [2].

When data are available on feed item consumption and on residue levels in feed commodities (required from registrants when the pesticide is registered for use), a 'dairy cow dietary burden' can be calculated as the theoretical highest dose anticipated from the diet or as an equivalent concentration in the dry-weight diet.

In a typical lactating dairy cow feeding study, three groups of animals are dosed for 28 days with the study pesticide at rates of 1×, 3× and 10× the highest level anticipated in animal feed commodities. Throughout the 28 days, milk samples are periodically taken for residue analysis. At the end of the dosing period, animals are slaughtered and samples of muscle, fat and edible offal are collected for residue analysis. Dosing may continue for a longer interval if a plateau residue level is not achieved in 28 days. Metabolism studies will have already identified the nature of the residue and recommended which components of the residue should be included in the residue definition for chemical analysis.

Some animals from the highest dose group may be kept in a depuration phase after the dosing phase of the study, with residue monitoring of the milk to determine the rate of residue disappearance when the feed is free of residue.

Information about residue disappearance rates is very useful to farmers and regulators managing situations where animals have become contaminated from their feed, or where animals have grazed pastures subjected to spray drift or have suffered other inadvertent exposure.

Not all studies have included a depuration phase.

The OECD Guidance Document [2] notes:

> "If the original study does not contain a depuration phase, it might be necessary in some cases to generate additional data to provide information on the potential decline of the residue levels within that depuration period. For animal welfare reasons, it should be thoroughly investigated whether a repeat of the full study is warranted. Where possible the missing information should be provided in a bridging study by using a testing scheme requiring a smaller number of test animals compared to the full study."

This paper explains how the milk residue behaviour in the depuration phase may be predicted from the milk residue data in the dosing phase.

Abbreviations: JMPR, Joint FAO/WHO Meeting on Pesticide Residues; LOQ, limit of quantification; OECD, Organisation for Economic Co-operation and Development; ppm, parts per million

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[1] Previously.

https://doi.org/10.1016/j.comtox.2018.02.001
Received 27 April 2017; Received in revised form 7 February 2018; Accepted 13 February 2018
Available online 19 February 2018

Theory

During the dosing phase, residue concentrations in the milk will depend on two processes:

1) The daily dose should add a constant increment of residue concentration (ΔC) each day; and
2) The metabolism, excretion and secretion of residue should, each day, remove a constant proportion (P) of the sum of the accumulated residues.

During the depuration phase, the dosing has stopped, but the removal of a constant proportion (P) of the accumulated residues should continue each day.

This means that the data obtained during the dosing phase should contain the information about the behaviour in the subsequent depuration phase. The aim is to analyse the data and extract the information suitable for extrapolation to the depuration phase.

The residue concentration in milk during dosing would be expected to rise rapidly following the dose and to fall more slowly at other times, i.e. the concentration in milk would not be a continuous function of time. The usual methods for regression line or curve fitting to experimental data are not suitable here because the supporting calculations rely on the application of calculus to continuous curves. So, another approach is required.

Mathematical sequence

We may establish a mathematical sequence, where each term represents the situation on each day of the study. We calculate each term, after the first, from the previous one.

$X_1 = \Delta C$

$X_{k+1} = \Delta C + (1-P)X_k$ during dosing

$X_{k+1} = (1-P)X_k$ after dosing has ceased.

X_k: residue concentration[2] (mg/kg), k^{th} term of the mathematical sequence; ΔC: increment of residue concentration (mg/kg) each day attributed to the daily dose; P: constant proportion of the residue dissipated in a day.

We should obtain the best estimates of ΔC and P from the experimental data by 'sequence fitting,' i.e. by finding values of ΔC and P that most closely fit the mathematical sequence to the data.

I have no mathematical formula for directly calculating ΔC and P.

In a process of successive approximation, a spreadsheet calculates the sum of squares of differences between the data and the mathematical sequence and the best fit is achieved by adjusting estimates for ΔC and P to achieve a minimum for the sum of squares. The spreadsheet also calculates combinations of small changes to ΔC and P and suggests values that improve the fit.

Half-life calculation

For a first order reaction $C = C_0 \times \exp(-jt)$ i.e. $\ln\left(\frac{C}{C_0}\right) = -jt$, where j is the rate constant.

For t= 1 day, $\frac{C}{C_0} = 1-P$ i. e. $\ln\left(\frac{C}{C_0}\right) = \ln(1-P)$

Therefore $\ln(1-P) = -j$

For half-life, $t_{1/2}$, $\frac{C}{C_0} = 0.5$ i. e. $\ln(0.5) = -jt_{1/2}$

i.e. $t_{1/2} = \frac{\ln(0.5)}{-j} = \frac{\ln(0.5)}{\ln(1-P)}$

A calculation from the P value of the fitted mathematical sequence produces the half-life for disappearance of residues in the depuration phase.

Plateau residue concentration

$x_{k+1} = \Delta C + (1-P)x_k$

When the plateau residue concentration is reached,

$x_{k+1} = x_k$

i.e. $x_k = \Delta C + x_k - Px_k$

i.e. $\Delta C = Px_K$

plateau residue $x_K = \frac{\Delta C}{P}$

Materials and methods

Worked example

In a dairy cow feeding study, fenpropathrin was administered to cows (group of four animals) for 28 days with daily doses equivalent to 250 ppm[3] in their diet [3]. Milk samples were analysed periodically for fenpropathrin residues. Table 1 and Fig. 1 summarise the residue data (mean of 4 animals) and the fitted sequence. Three animals were slaughtered on day 28 for tissue collection. Milk from the remaining animal was collected on day 31 to observe residue decline in the depuration phase.

The sum of the squares of differences between the mean residues and the calculated values (Table 1) is minimized to achieve the best fit of the sequence. The sequence must have a calculated value for each day, but differences are calculated only for those days where measured residues are available.

The data from day 1 to day 28 were used for sequence fitting and generated the parameters: ΔC = 0.176 mg/L; P = 0.517 (equivalent to a half-life of 0.95 days).

The decline of residues in milk from 0.24 to 0.04 mg/L obtained from one cow on days 28–31 was equivalent to a half-life of 1.2 days.

Calculating the parameters ΔC and P

The aim is to find the values of ΔC and P for the best fit of the mathematical sequence to the data. The calculation relies on a process of successive approximation.

Starting values for ΔC and P do not influence the final results, but the value of P must be between 0 and 1.

Successive approximation is achieved by choosing ΔC and P amendments that progressively reduce the sum of squares of differences between observed and calculated residue concentrations in the milk.

A spreadsheet calculates sums of squares for 9 sequences with controlled variations of the current approximation parameters (ΔC and P), e.g. we may begin with 20% variation of the parameter starting values.

[2] Some literature references express residue concentrations in milk as mg/L rather than mg/kg.

[3] The FAO Manual [4] explained the use of 'ppm'.
"express feed concentrations of active ingredients in feeding trials as ppm. This convention is used to avoid confusion between mg/kg feed and mg/kg body weight."